IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the Application of: Joan S. Steffan

Application No.: 10/789,518 Examiner: Aditi Dutt

Filed: February 27, 2004 Docket No.: R1:00047

For: METHODS AND REAGENTS FOR REDUCING POLYGLUTAMINE TOXICITY

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Appeal from Group 1649

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This is an Appeal Brief from the Final Rejection of claim 19 in the Office action mailed July 26, 2007.

(i) *Real party in interest*

The real party in interest is The Regents of University of California, the assignee of record.

(ii) *Related appeals and interferences.*

At the time of filing of the Appeal Brief, Appellant is not aware of any prior and pending appeals, judicial proceedings or interferences related to, directly affecting or that are directly affected by or have a bearing on the Board's decision in the pending appeal.

(iii) *Status of Claims.*

Appellants filed an Amendment dated April 10, 2007. The sole remaining pending claim was finally rejected in an Office action dated July 26, 2007. Therefore, Appellants submit that the claims listed in the Amendment dated March 5, 2007 are the appropriate subject of this appeal. The status of each of these claims is as follows:

- Claims 1 – 18 have been cancelled.
- Claim 19 has been rejected and is under appeal.
- Claims 20 – 77 have been cancelled.

(iv) *Status of Amendments.*

Appellants filed an Amendment dated April 10, 2007. The Final Office Action dated July 26, 2007 indicated that the Amendment was entered. Therefore, Appellants understand that the claims listed in the Amendment dated April 10, 2007, which were

finally rejected in the Office action dated July 26, 2007, are the claims that are on appeal.

(v) *Summary of claimed subject matter.*

Overview

The sole pending appealed claim relates to a method of treating Huntington's disease in a patient.

Independent claim 19

Independent claim 19 relates to a method of treating Huntington's disease in a patient by administering a therapeutically effective amount of a small ubiquitin-like modifier isopeptidase enhancer. A small ubiquitin-like modifier (SUMO) isopeptidase is a molecule that enhances the deSUMOylation of proteins. (A discussion of potential therapeutics including SUMO isopeptidase can be found in the specification at p. 13, line 16 to p. 14, line 14.) SUMOylation is a post-translational modification system that involves the attachment of SUMO-1 to lysine residues. This attachment can in turn affect the operation and degradation of proteins. (A discussion of the SUMOylation process and its role in HD pathogenesis can be found in the specification at p. 1, line 13 to p. 3, line 14.)

(vi) *Grounds of rejection to be reviewed on appeal.*

The grounds of rejection to be reviewed on appeal are:

- The objection to claim 19; and
- The rejection of claim 19 under 35 U.S.C. § 112 ¶ 1 as failing to comply with the enablement requirement.

(vii) *Argument.*

A. *The objection to claim 19.*

1. The objection.

Claim 19 was objected to based on the presence of the term "enhancer" at the end of the claim. The statement of objection was as follows:

> Regarding claim 19, the term 'enhancer' is not crossed off on the last line of the amended claim. Appropriate correction is required.

2. Response to objection.

Appellants believe there has been some misunderstanding with regard to the presence of the term "enhancer" at the end of claim 1. In Appellants' view this term is not in error. Specifically, Appellants always intended to pursue a treatment regime that comprised administering a SUMO isopeptidase enhancer, not merely a SUMO isopeptidase. For example, in the remarks from Appellants' April 10, 2007 Amendment Appellants state:

> Finally, Appellants have restricted the claims to recited [sic] only SUMO isopeptidase deSUMOylation enhancers, the very substance that were the subject of the studies disclosed in the current application. (4/10/07 Amendment, p. 7, 2nd paragraph)

Moreover, this comports with the disclosure of the application, which states in relevant part that:

> Potential therapeutic drugs include agents . . . which increase the activity of SUMO isopeptidase. (Specification, p. 13, lns. 30 to 36.)

It is possible that some of Appellants' comments were taken out of context. For example, Appellants wrote that they had amended the claims to recite a treatment of Huntington's disease "using a SUMO isopeptidase." However, Appellants meant by this comment that the treatment would occur because of the enhancement of these SUMO

isopeptidases, not that Appellants were suggesting the direct administration of SUMO isopeptidase, as such a treatment regime is never described in the disclosure.

3. Conclusion

In light of the above, Appellants respectfully submit that the objection of claim 19 should be withdrawn on the basis that the intention was always to seek protection for SUMO isopeptidase enhancers, not SUMO isopeptidases themselves, and that this intention is clearly supported by the disclosure of the application and Appellants' comments during the prosecution of the application.

B. The rejection of claim 19 under 35 U.S.C. § 112 ¶ 1.

1. The rejection.

Claim 19 was rejected under 35 U.S.C. § 112 ¶ 1 as failing to comply with the enablement requirement. The statement of the rejection was as follows:

> Due to the large quantity of experimentation necessary to treat HD by administration of any SUMO isopeptidase; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which has yet to determine an ideal model for treatment of Huntington's Disease and, the unpredictability of using invertebrate models for actual treatment in humans, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

2. Statement of relevant legal authorities

The first paragraph of 35 U.S.C. § 112 provides (emphasis added):

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The enablement requirement in 35 U.S.C. § 112 ¶ 1 demands that a patent's specification describe a claimed invention in sufficient detail that one skilled in the art can make and use the claimed invention. However, to comply with 35 U.S.C. 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003).

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which posed the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with

information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

3. Response to rejection

Claim 19 was rejected under 35 U.S.C. § 112 ¶ 1 on the basis that the use of SUMO isopeptidase enhancers to treat Huntington's disease is not enabled by the disclosure set forth in the specification. Specifically, the Examiner made final two specific rejections:

- That there is insufficient disclosure to enable one to use all possible SUMO isopeptidases to treat Huntington's disease; and
- That the fly model used is insufficient to enable one to treat Huntington's disease in humans with drugs that affect SUMO isopeptidase.

The Question of Enablement on Use of "SUMO isopeptidases"

First with regard to the Examiner's rejection of claim 19 based on the inclusion of all SUMO isopeptidases, as discussed above, Appellants have never sought such subject matter. Indeed, Appellants have specifically set forth that the treatment methodology they seek is one which relies on the administration of SUMO isopeptidase *enhancers*. (Specification, pg. 13, lns 30 to 35; and also pg. 29, lns. 1 to 6.) Regardless, Appellant will attempt, at least in a preliminary way, to address the thrust of the Examiner's rejection, namely, that there are so many different types of SUMO isopeptidases that one of ordinary skill in the art would not have been able to predict from the instant specification that all such possible SUMO isopeptidase [enhancers] would operate to treat Huntington's disease.

The current invention is directed to the treatment of Huntington's disease by enhancing deSUMOylation. It is undisputed by the Examiner that both the studies provided in the specification, as well as other published studies, have shown consistently that "a reduced function *smt3* (*Drosophila* SUMO) mutant results in a suppression of lethality and of neurodegeneration", both generally, and specifically with regard to Huntington's disease. (See, Specification, pg. 13, lns. 7 to 11 and pg. 21, ln. 24 to pg. 25, ln. 22; Steffan et al., *Science*, 413, 739 (2001). Likewise Appellants' studies, supported by the art and undisputed by the Examiner, show that suppression of SUMOylation or enhancement of deSUMOylation reduce polyglutamine toxicity, which clearly indicates a therapeutic effect in polyglutamine-repeat diseases such as Huntington's disease. (Specification, pg. 14, lns. 15 to 27 and pg. 25, ln. 24 to pg. 27, ln. 21.) Most significantly, Appellants provide results from studies on a Huntington's disease fly model which shows specifically that decreased SUMOylation decreases neurodegeneration from Huntington's disease. (Specification, pg. 27, lns. 24 to 33) In turn, it is well-established by both this application and the supporting art that increased levels of SUMO isopeptidase acts to enhance deSUMOylation. (See, Specification, pg. 25, lns. 13 to 20; and Melchior, Annu. Rev. Cell Dev. Biol., 16, 591, (2000))

Accordingly, Appellants would submit that one of ordinary skill in the art, having read the study results presented in the application would have been without doubt that administering agents known to enhance the activity of SUMO isopeptidases would have had a therapeutic effect on neurodegenerative diseases generally, and Huntington's disease specifically. Moreover, Appellants' application specifically studied the therapeutic effect of enhanced SUMO isopeptidase activity on organisms specifically designed to model the physiological impacts of Huntington's disease. With respect to this point Appellants would again stress that the test is not whether the specification contains an actual disclosure of how one of ordinary skill in the art would treat humans

using every SUMO isopeptidase enhancer, only whether one of ordinary skill in the art would have been able to develop therapeutic treatments without undue experimentation given the very detailed and focused results provided by Appellants. Focusing on this, the most salient question in any section 112, paragraph 1 inquiry, Appellants would submit that the Examiner has not provided any argument or evidence that would suggest that determining appropriate SUMO isopeptidase enhancers would entail undue experimentation.

Question of the Adequacy of Appellants' Drosophila Model

Appellants now address the Examiner's final point of rejection, namely that the *Drosophila* model for Huntington's disease used herein was insufficient to enable one of ordinary skill in the art to develop a treatment regime for Huntington's disease in humans, even using the specific SUMO isopeptidases described in the instant application. More specifically, the Examiner cites to a Wang et al. reference as teaching that fly models are insufficient, and that "proof of efficacy in mammalian models is considered a prerequisite before considering possible testing in humans." (Wang et al., page 1297, col. 2, para. 2.) The Examiner asserts from this generic statement that the use of the specific *Drosophila* model used in the instant application would not be considered sufficient by one of ordinary skill in the art to enable the development of a treatment regime for Huntington's disease in humans.

However, in the Final Office Action the Examiner also concedes that "the Drosophila fly model is extensively used for studying different aspects of neurodegenerative diseases in humans and expresses genes that mimic the pathology in mammalian systems." (Final Office Action, p. 4.) The Examiner also agrees that "the Drosophila provides a 'cost-effective platform for testing large matrices of drug combinations.'" The sole point of dispute appears to be that the Examiner does not believe the fly model can be used for determining a method of treatment of

Huntington's disease directly, and that "the proof of efficacy in mammalian models is considered as a prerequisite before considering possible testing in humans." (Final Office Action, p. 4) Indeed, much of the Examiner's Final Office Action reiterates this single point by quoting language from publications written by the inventors that stress the pre-therapeutic nature of the results obtained from the fly model disclosed in the application.

In the spirit of reducing the number of extraneous issues in the current case, Appellants have previously, and will again acknowledge that it is not possible to know absolutely whether something will work in a human until it is actually tested in humans. Appellants will further agree that it is well-established that prior to human testing mammalian models are not only needed, but mandated by law. However, for the purposes of a patentability inquiry the Examiner's statement of the legal test simply does not comport with the requirements for enablement set forth by the courts. Indeed, the Examiner's test does not even comply with the standards provided by the Manual of Patent Examination Practice (MPEP). Specifically, MPEP Section 2164.02 makes it explicitly clear that a "working example", in this case an actual therapeutic model, is not necessary, stating:

> An Appellant need not have actually reduced the invention to practice prior to filing. In *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date, no person had built a light amplifier or measured a population inversion in a gas discharge. The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)). (MPEP, §2164.02.)

In this case Appellants have submitted a number of working examples, including data on the efficacy of a SUMO isopeptidase enhancer in treating Huntington's disease in a fly model. The Examiner disputes that one of ordinary skill in the art would have

been able to correlate these results with treatments in humans, because Appellants used a fly model rather than a mammalian model. In short, the Examiner has set mammalian tests as a threshold for enabling a therapeutic claim. Appellants believe that this position is simply not supported by the law. The MPEP discusses "correlation" in Section 2164.02, where it states in relevant part:

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. . . . If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
>
> . . .
>
> A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). (MPEP § 2164.02.)

In short, nowhere do the courts or the MPEP require an "exact" correlation between the examples and the claimed invention as long as the particular model is "recognized as correlating." In fact, in evaluating the enablement of inventions relating to therapeutics Section 2107.03 places special emphasis on this point, stating:

> As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An

> Appellant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The Appellant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980). (MPEP, § 2107.03.)

In the current application, the Appellants report the results of a number of experiments on the disputed fly model that clearly show the efficacy of the claimed therapeutic. In addition, Appellants have provided corroborating data showing that the specific fly model used by Appellants, and other fly models as well, are commonly used in the neurodegenerative field to study the effectiveness of therapeutics, and have been used successfully to predict therapeutic treatments in humans for a number of disorders. (See, e.g., Appellants' 4/10/2007 Amendment, pgs. 8 to 12.) Finally, in his Final Office Action the Examiner explicitly "acknowledges" and "agrees" that the Appellants' Drosophila fly model is "extensively used for studying different aspects of neurodegenerative diseases" and "a cost-effective platform for testing large matrices of drug combinations." Appellants would submit that this should be sufficient to show that "one of skill in the art" would have considered there to be a "reasonable correlation" between Appellants' tests and a therapeutic treatment.

In contrast, the Examiner cites to a single reference (Wang et al.), which never actually disputes the validity of these fly models, but rather states that "by every measure flies expressing mutant human genes present with pathology that mimics the human disease in every important way." (Wang et al., page 1295, 1st column, 2nd paragraph.) Indeed, nowhere does the Examiner ever provide any prior art that

specifically calls into question the validity of Appellants' fly model in predicting the efficacy of Huntington's disease treatments, or the recognized correlation of results from Appellants' fly model to Huntington's disease. As such, Appellants would submit that the Examiner's continued dismissal of the working examples of the current application is unwarranted and would, if upheld, improperly raise the enablement standard for claims to human treatments far in excess of the standard set forth repeatedly by the courts.

4. Conclusion

In light of the above, Appellants respectfully submit that the rejection of claim 19 under 35 U.S.C. § 112 ¶ 1 should be withdrawn on the basis that the specification provides sufficient supporting disclosure that one of ordinary skill in the art would have been enabled to make or use the invention of claim 19.

Respectfully submitted,

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(viii) *Claims appendix.*

19. (Previously presented) A method of treating Huntington's disease in a patient, comprising administering to a patient diagnosed with Huntington's disease a therapeutically effective amount of a small ubiquitin-like modifier isopeptidase enhancer.

(ix) *Evidence appendix.*

1. Steffan et al., "Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration-dependent in *Drosophila*", Nature, October 18, 2001, Vol. 413, pp. 739-743. First entered into the record in IDS filed January 28, 2005.
2. Melchior, "SUMO – Nonclassical Ubiquitin", Annu. Ref. Cell. Dev. Biol. 2000, Vol. 16, pp 591-626. First entered into the record in IDS filed January 28, 2005.
3. Wang et al., "Animal models of Huntington's disease: Implications in uncovering pathogenic mechanisms and developing therapies', Acta Pharmacologica Sinica, October 27, 2006, Vol. 10, pp. 1287-1302. First entered into the record in the Office Action dated November 16, 2006

(x) *Related proceedings appendix.*

None.